

# Functional area of the brain And Mapping Brain Asymmetry

## Abstract

When people talk about "**the brain**," they are generally referring to the **cerebral hemispheres**. The outer layer, the **cerebral cortex** is responsible for sensory perception, movement, language, thinking, memory, consciousness, and certain aspects of emotion. In short, we need the intact cerebral hemispheres to adapt to our ever-changing external environment.

**Brain asymmetry** has been observed in animals and humans structurally, functionally, and behaviorally. This lateralization is thought to originate from evolutionary, hereditary, developmental, experiential and pathological factors. This paper reviews the diverse literature describing brain asymmetry, focusing primarily on those observations characterizing anatomical differences between the hemispheres.

## Functional area of the brain :

### Different parts of the cortex have different functions :

Some parts have a predominantly **motor** function, whereas other parts are receiving areas for one of the major **sensory systems**. Most of the cerebral cortex in humans has an "**association function**," a term that can perhaps be explained functionally as interrelating the various activities in the different parts of the brain.

**The basic division** of each of the hemispheres is into **four lobes**: frontal, parietal, temporal, and occipital. Two prominent fissures allow this subdivision to be made the central fissure and the lateral fissure. The **central fissure** divides the area anteriorly, the frontal lobe, from the area posteriorly, the parietal lobe. The parietal lobe extends posteriorly to the parieto-occipital fissure (see Figure 1). The brain area behind that fissure is the occipital lobe. The temporal lobe and the lateral fissure cannot be seen on this view of the brain (see next illustration).

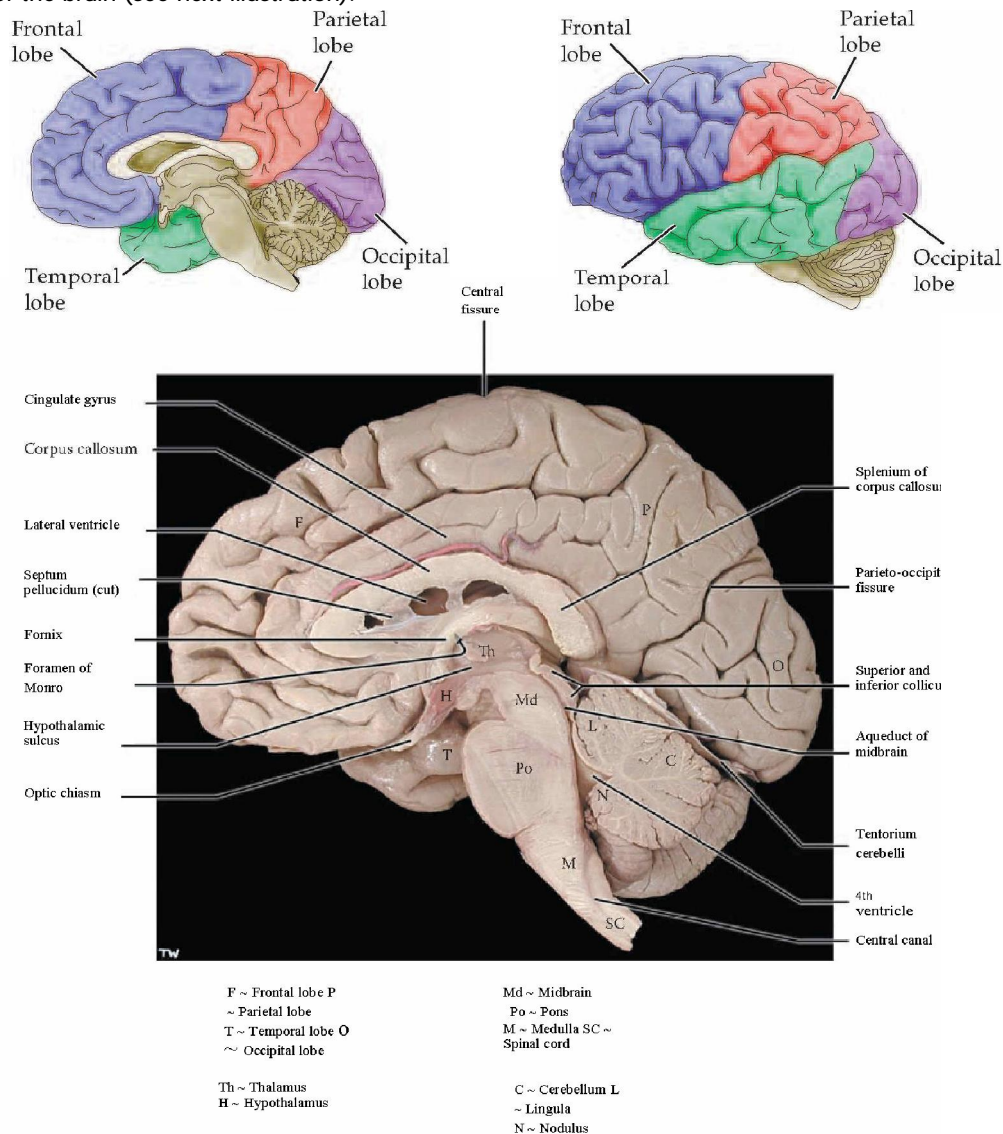


FIGURE 1 : Cerebral Hemispheres 7 - Medial View (photograph)

**Some cortical areas are functionally directly** connected with either a sensory or motor system; these are known as the primary areas. The gyrus in front of the central fissure is called the precentral gyrus, also called area 4, and it is the primary motor area, specialized for the control of voluntary movements. The area in front of this gyrus is called the (lateral) premotor area, also called area 6, which is likewise involved with voluntary motor actions. An area in the frontal lobe (outlined) has a motor function in regards to eye movements; this is called the frontal eye field (area 8). The gyrus behind the central fissure is the postcentral gyrus, including areas 1, 2 and 3, and it has a somatosensory function for information from the skin (and joints). (Other sensory primary areas will be identified at the appropriate time).

**The remaining cortical areas that are not directly** linked to either a sensory or motor function are called association cortex. The most anterior parts of the frontal lobe are the newest in evolution and are known as the prefrontal cortex (in front of the frontal eye fields previously mentioned). This broad cortical area seems to be the chief "executive" part of the brain. The parietal areas are connected to sensory inputs and have a major role in integrating sensory information from the various modalities. In the parietal lobe, there are two special gyri, the supramarginal and angular gyri; these areas, particularly on the nondominant side, seem to be involved in visuospatial activities.

**Some cortical functions are not equally divided** between the two hemispheres. One hemisphere is therefore said to be dominant for that function. This is the case for language ability, which, in most people, is located in the left hemisphere. This photograph of the left hemisphere shows the two language areas: Broca's area for the motor aspects of speech and Wernicke's area for the comprehension of written and spoken language (near the auditory area).

### CLINICAL ASPECTS

It is most important to delineate anatomically the functional areas of the cortex. This forms the basis for understanding the clinical implications of damage (called lesions) to the various parts of the brain. Clinicians are now being assisted in their tasks by modern imaging techniques, including CT and MRI.

**The lateral fissure** has been "opened" to reveal some buried cortical tissue; this area is called the **insula**. The function of this cortical area has been somewhat in doubt over the years. It seems that this is the area responsible for receiving taste sensations, relayed from the brainstem. Sensations from our internal organs may reach the cortical level in this area.

The specialized cortical gyri for hearing (audition) are also to be found within the lateral fissure, but they are part of the upper surface of the superior temporal gyrus.

It should be noted that the lateral fissure has within it a large number of blood vessels, which have been removed -branches of the middle cerebral artery (discussed with Figure 58). Branches to the interior of the brain, the striate arteries, are given off in the lateral fissure. The insular cortex can be recognized on a horizontal section of the brain and also on coronal views of the brain, as well as with brain imaging (CT and MRI).

### CLINICAL ASPECT

A closed head injury that affects the brain is one of the most serious forms of accidents. The general term for this is a concussion, a bruising of the brain. There are various degrees of concussion depending upon the severity of the trauma. The effects vary from mild headache to unconsciousness and may include some memory loss, usually temporary.

## Functions of the Cerebral Lobes :

Lobe	Functions
Frontal	Voluntary motor control of skeletal muscles: personality: higher intellectual processes (e.g. concentration, planning, and decision making): verbal communication
Parietal	Somesthetic interpretation (e.g. cutaneous and muscular sensations): understanding speech and formulating words to express thoughts and emotions: interpretation of textures and shapes
Temporal	Interpretation of auditory sensations: storage (memory) of auditory and visual experiences
Occipital	Integration of movements in focusing the eye: correlation of visual images with previous visual experiences and other sensory stimuli; conscious perception of vision
Insula	Memory: integration of other cerebral activities

Portions of **the precentral gyrus** responsible for **motor movement** and portions of **the postcentral gyrus** that respond to **sensory stimuli** do not correspond in size to the part of the body being served, but rather to the number of motor units activated or to the density of receptors (fig.2). For example, because the hand has many motor units and sensory receptors, larger portions of the precentral and postcentral gyri serve it than serve the thorax, even though the thorax is much larger. In addition to responding to somatesthetic stimuli, the parietal lobe functions in understanding speech and in articulating thoughts and emotions. The parietal lobe also interprets the textures and shapes of objects as they are handled.

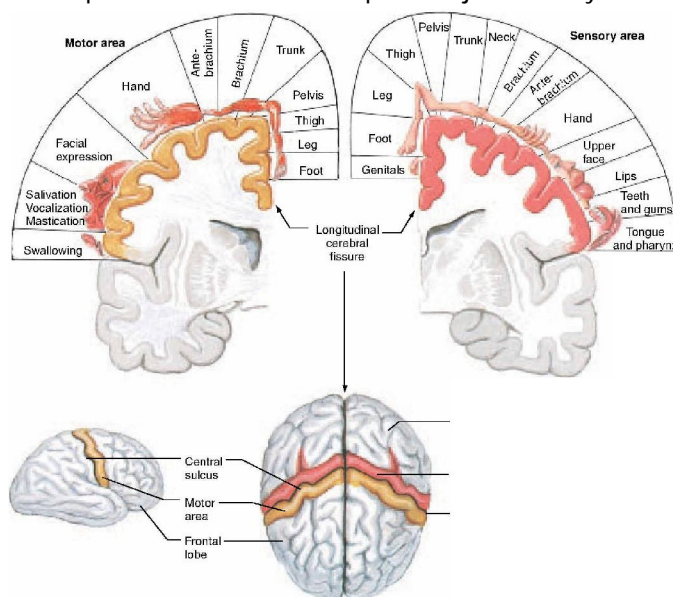


FIGURE 2 Motor and sensory areas of the cerebral cortex. Motor areas control skeletal muscles and sensory areas receive somatesthetic sensations.

## Temporal Lobe

The temporal lobe is located below the parietal lobe and the posterior portion of the frontal lobe. It is separated from both by the lateral sulcus (see fig. 3). The temporal lobe contains auditory centers that receive sensory fibers from the cochlea of the ear. This lobe also interprets some sensory experiences and stores memories of both auditory and visual experiences.

## Occipital Lobe

The occipital lobe forms the posterior portion of the cerebrum and is not distinctly separated from the temporal and parietal lobes (see fig. 3). It lies superior to the cerebellum and is separated from it by an infolding of the meningeal layer called the tentorium cerebelli. The principal functions of the occipital lobe concern vision. It integrates eye movements by directing and focusing the eye. It is also responsible for visual association-correlating visual images with previous visual experiences and other sensory stimuli.

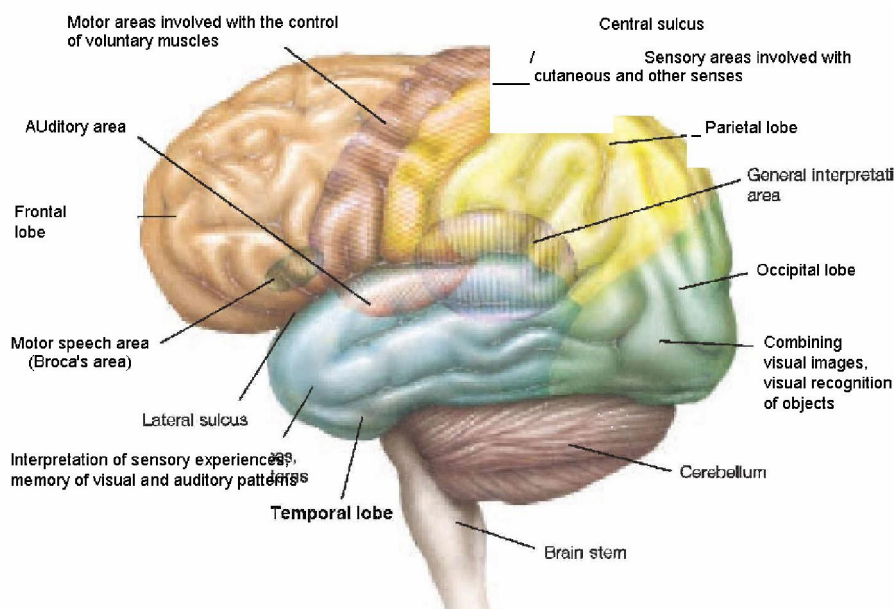


FIGURE 3 The lobes of the left cerebral hemisphere showing the principal motor and sensory areas of the cerebral cortex.

# Mapping Brain Asymmetry

## Introduction

Most biological systems demonstrate some degree of asymmetry

1. From humans to lower animals, normal variation and **specialization produce asymmetries of function and structure**. Even gross external features of the face and extremities evidence this asymmetry
2. In humans and many other mammals, the two brain hemispheres differ in their anatomy and function. While cursory examination of the gross features of the human brain fails to expose profound left/right differences, careful examination of its structure reveals a variety of asymmetric features. This lateralized specialization is thought to originate from evolutionary, developmental, hereditary, experiential and pathological factors. For example, the evolutionary expansion of the left-hemisphere language cortices, in particular, may have led to marked volume asymmetries in **Broca's speech area**, the planum temporale (an auditory processing structure in the posterior temporal lobe), and in other structures crucial for speech production, perception, and motor dominance. Asymmetries in the brain's functional layout, **cytoarchitecture**, and neurochemistry have also been correlated with asymmetrical behavioral traits, such as handedness, auditory perception, motor preferences, and **sensory acuity**. Here, we review a variety of methods and their resulting observations about the structural and functional asymmetries in the brain with a particular focus on anatomic differences. Brain mapping approaches, in particular, can detect and visualize patterns of asymmetries in whole populations, including subtle alterations in disease, with age, and during development. These and other tools show great promise for assessing factors that modulate cognitive specialization in the brain, including the ontogeny, phylogeny and genetic determinants of brain asymmetry.

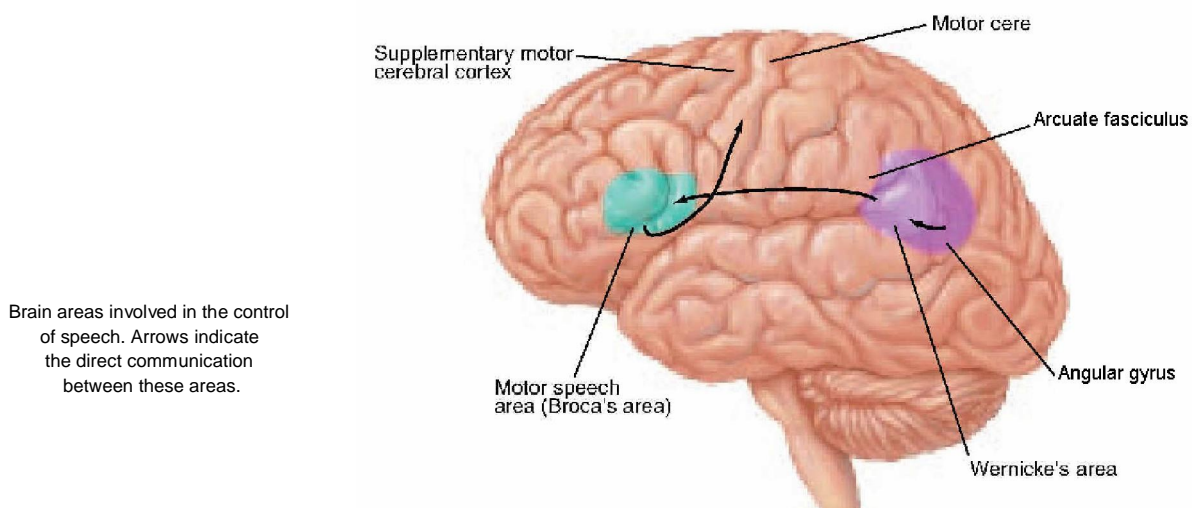
## Language And Handedness

Knowledge of the brain regions involved in language has been gained primarily by the study of aphasia-speech and language disorders caused by damage to specific language areas of the brain. These areas are generally located in the cerebral cortex of the left hemisphere in both right-handed and lefthanded people.

The motor speech area (Broca's area) is located in the left inferior gyrus of the frontal lobe. Neural activity in the motor speech area causes selective stimulation of motor impulses in motor centers elsewhere in the frontal lobe, which in turn causes coordinated skeletal muscle movement in the pharynx and larynx. At the same time, motor impulses are sent to respiratory muscles to regulate air movement across the vocal folds. The combined muscular stimulation translates thought patterns into speech. Wernicke's (ver'n-ke-z) area is located in the superior gyrus of the temporal lobe and is directly connected to the motor speech area by a fiber tract called the arcuate fasciculus. People with Wernicke's aphasia produce speech that has been described as a "word salad." The words used may be real words that are randomly mixed together, or they may be made-up words. Language comprehension has been destroyed in people with Wernicke's aphasia; they cannot understand either spoken or written language.

It appears that the concept of words to be spoken originates in Wernicke's area and is then communicated to the motor speech area through the arcuate fasciculus. Damage to the arcuate fasciculus produces conduction aphasia, which is fluent but nonsensical speech as in Wernicke's aphasia, even though both the motor speech area and Wernicke's area are intact.

The angular gyrus, located at the junction of the parietal, temporal, and occipital lobes, is believed to be a center for the integration of auditory, visual, and somesthetic information. Damage to the angular gyrus produces aphasia, which suggests that this area projects to Wernicke's area. Some patients with damage to the left angular gyrus can speak and understand spoken language but cannot read or write. Other patients can write a sentence but cannot read it, presumably because of damage to the projections from the occipital lobe (involved in vision) to the angular gyrus





**Handedness.** The relationship between brain asymmetry and handedness has sparked considerable interest and debate<sup>10-12</sup>. A rightward hand preference might be expected to result from, or even induce, asymmetries in the motor cortex. Even so, motor cortex asymmetries are quite subtle<sup>13</sup>. Intriguingly, hand preference correlates more strongly with structural and functional asymmetries in language processing structures such as the planum temporale and other primary auditory and association cortices surrounding the Sylvian fissures. Language dominance and handedness are not perfectly correlated either. Right-handers (but not left-handers) typically display a strong leftward specialization for speech and language comprehension<sup>14</sup>. Approximately 97% of right-handers have their speech and language localized to the left hemisphere, while only 3% demonstrate a right-hemisphere lateralization or bilateral language representation. These relationships degrade to only 70/30 in left-handed individuals<sup>15</sup>. Thus, some right-handed patients have a right-hemisphere dominance for language, while left-handers may display a leftward dominance<sup>16</sup>.

Clearly, brain asymmetry, language laterality and handedness are interrelated but in a complex way<sup>17-19</sup>. Many factors affect these gradients, including genetics<sup>20, 21</sup>, developmental events (Grimshaw et al., 1985), neurochemical asymmetries<sup>23</sup> (see Inset Box 1), experience and disease.

[Inset Box 1]

### Neurochemical Asymmetries

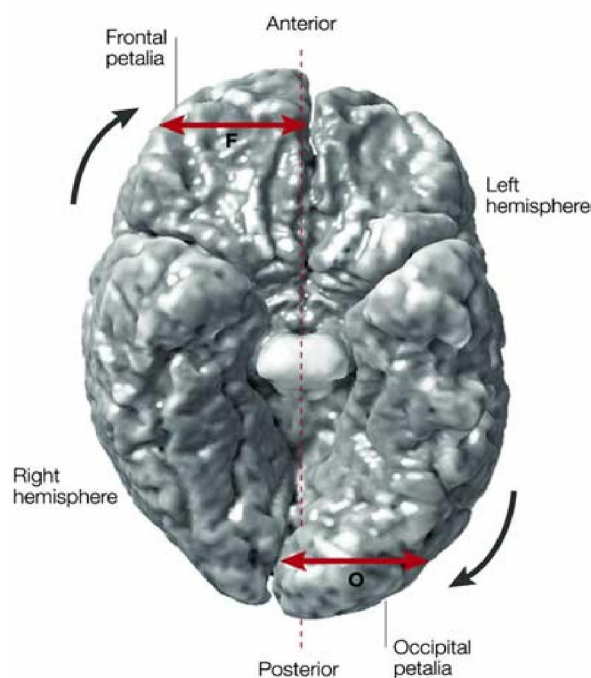
*Some investigators have linked chemical asymmetries with the specialized functional roles of the two hemispheres. Tucker and Williamson<sup>24</sup> argued that the left and right hemispheres are relatively rich in processes that depend on dopamine and norepinephrine, respectively. Autopsy studies show a leftward asymmetry in dopamine levels in the globus pallidus<sup>23</sup> and so do radioligand PET scans of the basal ganglia<sup>25</sup>. Noradrenergic neurons are also strongly lateralized in the thalamus, being relatively abundant in the right ventral-lateral nuclei<sup>26</sup>.*

*Glick et al. also noted behavioral asymmetries that mirrored these neurotransmitter differences: dopaminergic drugs induced motor changes in rats causing them to circle strongly in one direction. This behavioral asymmetry was proportional to the asymmetry in dopaminergic activity, as well as nigrostriatal dopamine sensitivity. Tucker and Williamson<sup>24</sup> proposed that the left hemisphere became organized around a dopamine activation system, which made it superior for complex motor programming (leading to a right manual preference), and speech. They further argued that the right hemisphere became organized around a noradrenergic arousal system. This maintains alertness, orients the individual to new stimuli, and integrates bilateral perceptual information. The idea that the hemispheres perform analytical (left) and holistic (right) processing is an old one, and is hotly debated<sup>19</sup>. Nonetheless, the idea that specific neurochemical asymmetries lead to cognitive specialization is readily testable. It also leads to tantalizing links between molecular and behavioral asymmetries. Other models of laterality<sup>27, 2</sup> suggest that the left hemisphere is specialized for specific types of motor function, verbal and non-verbal, and that the lateralization of language emerged from the leftward dominance over motor function.*

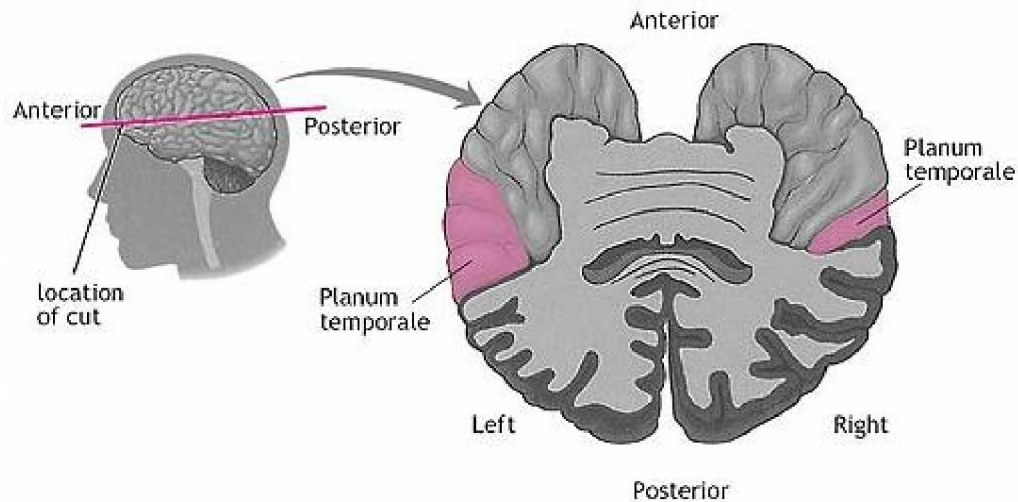
[Inset Box 1 ended here]

### Macroscopic Anatomical Asymmetries

Petalia and Yakovlevian torque. Gross anatomical asymmetries in the brain have been observed for over a century<sup>28</sup>. More recently, numerous structural MRI studies have documented anatomical differences between the hemispheres. These investigations of asymmetry focus most frequently on the planum temporale because of its relationship to handedness and language laterality (see also Inset Box 2: Asymmetries in Microscopic Anatomy).



## Asymmetries in Microscopic Anatomy



*Cytoarchitecture. Asymmetries in brain organization are also found at the cellular level. Cytoarchitectural studies by Galaburda et al.<sup>29</sup> found a perfect rank-order correlation between gross planum temporale asymmetry and the area of the cellular field Tpt, which is located on and around the planum. This cellular field is implicated in higher-order auditory functions. Similar asymmetries were found for parietal architectonic regions (e.g., language area PG30). The magnitude of planum asymmetries also correlates negatively with the total size of the planum (left plus right). This means that rather than having extra tissue, people with planar asymmetries usually have volume reductions (and hypothetically, fewer neurons) on one side, relative to individuals with symmetrical plana. Using [3H]-thymidine techniques to label neurons undergoing their last mitosis, Rosen et al.<sup>31</sup> found that there were no subsequent hemispheric differences in labeling ratios between left and right sides, regardless of degree of asymmetry. Cortical area asymmetries were therefore thought to result from earlier asymmetries, prior to cell labeling, in progenitor cell proliferation (and/or early cell death), rather than differences in post-migrational cell death (which would have led to subsequent differences in cell labeling). Such studies tracking cellular changes in cortical development implicate early developmental events in the formation of asymmetric cortical areas—specifically, events occurring during progenitor cell proliferation and/or death (i.e., before the birth of the first neuron), rather than during later neuroblast division<sup>31</sup>. Dendritic Arborization. A further provocative finding came in 1985 when Scheibel et al.<sup>32</sup> reported that the extent of high-order dendritic branching was greater in the left-hemisphere speech areas (including Broca's area) than in their homologs on the right. Lower order dendrites were, however, longer in the right hemisphere. The authors also noted the right hemisphere develops faster in the first year of postnatal life, but is eventually surpassed by the left hemisphere. In the first postnatal year, left-hemisphere language regions consistently lag behind their right-hemisphere homologs in their state of development, perhaps to await speech development<sup>33</sup>. The hemispheres may follow separate developmental programmes<sup>34</sup>, with a variety of physical asymmetries emerging in utero, in childhood and in the teenage years.*

[Inset Box 2 ends here]

Among the most prominent observations of brain asymmetry are the right frontal and left occipital petalias, or protrusions of the surface of one hemisphere relative to the other<sup>35</sup>. These impressions on the inner skull surface provide a negative of the brain's surface topology and a signature of regional hemispheric asymmetries. CT and MRI studies show that these petalias are more prominent in right-handers<sup>36, 37</sup>. Similar, but lesser, asymmetries are seen in phylogenetically older primates (and other species), as evidenced by endocasts from fossilized cranial bones (K. Zilles, personal comm.). Asymmetries seen in comparative studies provide strong evidence for phylogenetic origins of brain lateralization. The massive evolutionary expansion of the prefrontal cortex may, in part, reflect its role in speech production. Although the two brain hemispheres are similar in weight and volume, the distribution of tissue differs markedly between hemispheres. First, the right hemisphere protrudes anteriorly beyond the left, and the left hemisphere extends posteriorly beyond the right. A second feature, sometimes regarded as separate from the frontal and occipital protrusions (petalias), is that the right frontal/central region is often wider than the left, and the left occipital region is often wider than the right. These features of overall brain shape reflect lateralized volume differences in frontal ( $R > L$ ) and occipital regions ( $L > R$ ). Another prominent geometric distortion of the hemispheres is known as Yakovlevian anticlockwise torque. This encompasses the features described above, and includes the frequent extension of the left occipital lobe across the midline (over the right occipital lobe), bending the interhemispheric fissure towards the right. This general pattern is established prenatally,

**Perisylvian Asymmetry.** The asymmetric trajectory of the Sylvian fissure was one of the first anatomical asymmetries to be described<sup>28, 38</sup>. At its posterior limit, the right Sylvian fissure curves upward more anteriorly than the left, and the left has a gentler slope<sup>10</sup>. The height of the end-point of the Sylvian fissure is also negatively correlated with the volume of the planum temporale<sup>35</sup>. This region, in the posterior superior temporal lobe, is important for phonological encoding and speech perception, and is the epicenter of a mosaic of left hemisphere language regions. It analyzes the amplitude and frequency of sounds, as well as other acoustic information involved in speech perception. The planum shows marked leftward volume asymmetry<sup>39</sup> related to the degree of right-handedness<sup>40</sup>. Using an asymmetry index (AI) that corrects for total planum size ( $AI = (\text{right} - \text{left}) / 0.5(\text{right} + \text{left})$ ), Steinmetz<sup>41</sup> analyzed 154 MRI scans and found that right-handers exhibit greater planum asymmetry (mean  $AI = -0.30 \pm 0.28SD$ ;  $N=121$ ), while left-handers show a weaker, but still leftward, asymmetry (mean  $AI = -0.16 \pm 0.31SD$ ;  $N=33$ ). In this study, no gender effects or gender by handedness interactions were found, suggesting that these may be subtle if present<sup>42, 43</sup>. Although the left planum is an extension of Wernicke's posterior receptive language area, the planum asymmetry also appears in higher non-human primates (including chimpanzees<sup>44</sup>). Its dramatic increase in humans suggests a link with the evolution of language. In humans, the left planum is up to 10 times larger than its right-hemisphere counterpart, and is perhaps the most prominent and functionally significant human brain asymmetry<sup>41</sup>. Broca's speech area (in the left frontal lobe) is also larger in volume than its homolog in the right hemisphere<sup>45, 46</sup>. The greatest asymmetries of structure are clearly localized to the perisylvian language area. Hochberg and LeMay<sup>47</sup> studied the location of the posterior tip of the Sylvian fissure, and found that it was higher on the right in 67 of the 100 right-handers they studied, but only in 6 of 28 non-right-handers (i.e., 21%). Heschl's gyrus is also larger on the left side<sup>48</sup>, a feature attributed to greater amounts of underlying white matter<sup>49</sup>. These asymmetries are also found in children<sup>50, 51</sup>. Their magnitude increases throughout childhood and the teenage years, even after adjusting for developmental increases in brain volume<sup>52</sup>. This suggests that there may be hemispheric differences in white matter maturation, perhaps during the many regional growth spurts in myelination that occur in childhood<sup>53</sup>. In addition, exposure to gonadal steroid hormones during critical developmental periods may differentially affect the growth of each side of the brain. The anatomical connectivity of the anterior temporal and inferior frontal lobes is also thought to be more highly developed in the right hemisphere. The uncinate fasciculus, which connects these two regions, has been found to be asymmetrical in both sexes, being 27% larger and containing 33% more fibres in the right than the left hemisphere<sup>54</sup>.

**Sulcal Pattern Asymmetry.** In addition to the planum temporale, other gyral regions have received considerable attention in the quest to map the profile of cortical asymmetries. The central sulcus, which houses the primary motor cortex, was found to be deeper and larger in the right hemisphere of both males and females<sup>55</sup>. Positional asymmetries were gender specific, observed only in males. These measures remain controversial, as Amunts et al.<sup>56</sup> found the central sulcus to be deeper on the left, in males. Methodological differences and age effects may explain the inconsistencies. Nonetheless, clear motor asymmetries are found in regions that are more proximal to the motor effectors. The right cortico-spinal tract is larger than the left in 75% of subjects, and the left pyramid crosses more rostrally and is larger than the right in 82-87% of subjects<sup>57</sup>. In physiological studies of squirrel monkeys<sup>58</sup>, the sizes of cortical somatotopic areas representing the distal forelimb also depend on limb preference. The size of these areas is greater in the hemisphere opposite the dominant limb (see Inset Box 3: 'Why is the Brain Asymmetrical?'). It is not currently known how extensive these asymmetries are cytoarchitecturally.

[Inset Box 3]

**Q. Why is the brain asymmetrical?**

*A. Functional asymmetries in the brain were initially thought to be uniquely human, reflecting unique processing demands required to produce and comprehend language. Nonetheless, functional and structural asymmetries have been identified in non-human primates and many other species<sup>59</sup>. Passerine birds produce song primarily under left-hemisphere control<sup>60</sup> and Japanese Macaques exhibit a right-ear advantage for processing auditory stimuli<sup>61</sup>. Language is commonly lateralized to the left hemisphere, and some argue that this is advantageous: first, it avoids competition between hemispheres for control of the muscles involved in speech; second, it may be more efficient to transfer language information between a collection of focal areas in a single hemisphere. More asymmetrical brains, for example, have a corpus callosum with a reduced midsagittal area relative to more symmetrical ones<sup>62</sup>. This may reflect fewer and/or thinner fibers connecting the two hemispheres, perhaps due to differences in axonal pruning. The massive evolutionary expansion of the brain may have resulted in a level of complexity where duplication of structures was no longer efficient, relative to specialization of functions within a hemisphere. Time limits in callosal transfer of information between the brain hemispheres, in larger brains, may also favor development of unilateral networks.*

*The main pitfall in arguing that left-hemisphere dominance provides an evolutionary advantage is that bilateral language representation, or rightward dominance, are also common. In addition, leftward dominance does not, in general, provide a cognitive advantage<sup>63</sup>.*

*Others suggest that the left hemisphere's dominance over language evolved from its control of the right hand (an idea first proposed by Condillac in 1746): its programming of skilled movement and gesture may have evolved to encompass control of the motor systems involved in speech<sup>2</sup>. Broca's area, in particular, is a premotor module in the neocortex. It sequences complex articulations that are not limited to speech. Great apes, including chimpanzees, bonobos, and gorillas, also have*

*an enlarged area 44 (part of Broca's area). This area controls muscles of the face and vocal tract, although this area is not as massively interconnected with the homolog of Wernicke's area as it is in humans<sup>64</sup>. Cantalupo and Hopkins<sup>65</sup> suggest that non human primates developed a homolog of Broca's area due to a link between primate vocalization and gesture: captive apes usually gesture with the right hand as they vocalize. Lieberman<sup>66</sup> suggests that language is a relatively recent evolutionary adaptation (not more than 200,000 years old) that the Neanderthal vocal tract was incapable of articulating the range of modern human speech sounds.*

*Research on indigenous gestural languages invented by children in Taiwan<sup>67</sup> and in Nicaragua<sup>68</sup> provides some evidence for the innate relation between gesture and language. Functional neuroimaging studies also suggest that deaf subjects using a gestural sign language activate many of the systems involved in verbal language production<sup>69</sup>. These congruences in functional anatomy may support the hypothesis that verbal language evolved from gestural language as an outgrowth of the already asymmetric motor control system<sup>70</sup>.*

[End of Inset Box 3]

**Composite Brain Maps.** More recently, digital brain maps have visualized the profile of cortical asymmetries in 3 dimensions<sup>71</sup>, 13, 72 THERE IS an average representation of the primary sulcal pattern derived from MRI scans of 20 right handers<sup>73</sup> Using computational methods, 3D models of cortical sulci can be reflected in the interhemispheric plane, and the 3D distance can be computed between the mean structure on the left and a reflected version of the mean structure on the right. The magnitude of this asymmetry can then be plotted as a color-coded map. The degree of asymmetry is different in different parts of the brain (greater asymmetries are shown here in red). By comparing the average magnitude of these asymmetries with their standard error (or in 3D, their covariance field), regions with statistically significant asymmetries are readily identified .

As the maps indicate, the Sylvian fissure is, in general, longer in the left hemisphere than the right. Strikingly, some right-hemisphere structures are 'torqued forward' relative to the left. This is consistent with the direction of the petalia . in which the right frontal lobe juts forward relative to the left. Nonetheless, the effect is comparatively localized, and perisylvian structures exhibit the strongest asymmetries. Other studies have evaluated the incidence of sulci in one hemisphere relative to the other, compiling stereotaxic maps for the planum temporale in standardized atlas coordinates<sup>74</sup>. Paus et al.<sup>75</sup> generated a probabilistic map to describe the location of the cingulate and paracingulate sulci (when present) in each brain hemisphere. In MRI data from 247 healthy young volunteers, the paracingulate sulcus occurred more frequently in the left hemisphere<sup>75</sup>, a feature thought to be linked with the participation of the left anterior cingulate cortex in language tasks. Subsequent functional MRI studies

revealed that task related brain activation, during a word generation task, rarely extended into the cingulate sulcus when a prominent paracingulate sulcus was present, but if no paracingulate sulcus was present, these activations spread into the cingulate sulcus<sup>76</sup>. Group studies of functional anatomy rarely stratify their samples into groups with different normal anatomic variations, but such studies are needed to elucidate how these normal variants impact functional organization and cerebral asymmetries.

**Statistical Maps.** Besides examining sulci or other features of the brain's surface, voxel-based morphometric analyses have further characterized the extent of cerebral asymmetry<sup>77, 78</sup>. In this type of approach, the entire brain volume is assessed on a voxel by voxel basis with MRI. Avoiding manual delineations of regions of interest but requiring smoothed data (12 mm), these approaches are automated and enable efficient large-N studies. Good et al. <sup>77</sup> found significant asymmetries in grey and white matter distribution in the occipital, frontal, and temporal lobes, including Heschl's gyrus, the planum temporale and the hippocampus, and Watkins et al. <sup>78</sup> discovered previously undetected volume asymmetries, in both sexes, in the anterior insular cortex (R > L). In the largest MRI study to date, Good et al. <sup>77</sup> did not find a relationship between asymmetry and handedness, but did find several gender- related differences. Males exhibited a greater leftward asymmetry in the planum and Heschl's gyrus compared with females, consistent with the notion that brain structure is more lateralized in males than in females<sup>79</sup>.

**Mapping Asymmetry with Brain Atlases.** Building on these automated methods, digital brain atlases now compile brain data from hundreds, or even thousands of subjects <sup>80, 81</sup>. These tools empower large-scale studies of brain asymmetry, as they reveal how factors such as age<sup>52</sup>, gender<sup>43</sup>, and disease<sup>72</sup> affect or modulate these asymmetries (see below). Brain structure is so complex and variable that systematic asymmetries can be difficult to localize, and distinguish from random fluctuations. Population-based brain atlases surmount this problem by averaging 3D models of anatomy across subjects, while storing statistics on anatomic variation.

**Ventricular asymmetry** is an **example** of a statistically significant effect that becomes clear in a group average brain map, but is not universally apparent in individual subjects. It is, however, consistent with volumetric measures (e.g. Shenton et al.<sup>82</sup>). In normal subjects, occipital horns are on average around 17% larger on the left ( $4070 \pm 480 \text{ mm}^3$  vs.  $3475 \pm 334 \text{ mm}^3$ ;  $p < 0.05$ ), but no significant asymmetry is observed in the superior or inferior horns ( $p > 0.19, 0.37$ ). This ventricular asymmetry may reflect rapid, asymmetric growth in the overlying language systems; it can occasionally be seen in the embryonic brain, using ultrasound, as early as 29-31 weeks post conception<sup>83</sup>.



## ***Factors that Affect Anatomical Asymmetries***

**Fetal Orientation.** Previc<sup>84</sup> suggests that asymmetric influences in the prenatal environment, even due to fetal posture, may lead to perceptual and motor asymmetry. Two-thirds of fetuses are confined to a leftward fetal position in the third trimester, with their right side facing outwards. Lateralization of language perception may result from asymmetries in their auditory experience. The right ear may even be better positioned to discriminate high-frequency speech sounds. In an elaborate model of motor dominance, Previc<sup>84</sup> also argues that asymmetrical vestibular stimulation in utero may produce behavioral asymmetries later in life. In an intriguing epidemiological study, Kieler et al.<sup>85</sup> surveyed 179,395 men born in Sweden between 1973 and 1978, and concluded that ultrasound exposure in fetal life increases the chances of being left-handed, by about 30%. The controversial suggestion that routine prenatal ultrasound affects the fetal brain has stimulated further research into its potential effects on embryogenesis, as ultrasound exposure has not previously been associated with any childhood malignancy or behavioral sequelae.

**Heredity and Environment.** Embryonic processes that lead to functional and structural asymmetry of the language cortex are the focus of intense study, as their failure may lead to decreased functional specialization in the cortex. Schlaug et al.<sup>86</sup> also studied musicians with perfect pitch (i.e., the ability to identify any musical note without comparing it to a reference note). In musicians, planar asymmetry was twice as great as in non-musicians, and greatest of all in those with perfect pitch. Exaggerated asymmetries may therefore indicate increased capabilities in processing certain auditory features<sup>41</sup>. A follow-up study<sup>87</sup> revealed that the exaggerated asymmetry in the perfect pitch group was attributable to a smaller right (rather than an enlarged left) planum, relative to non-musician controls and musicians without perfect pitch. The absolute size of the right planum (not the left) predicted group membership, perhaps implying neurodevelopmental “pruning” of the right planum in musicians with perfect pitch. The authors pointed to a possible genetic determination for the increased planum asymmetry.

Recent genetic brain-mapping techniques, applied to MRI scan data from identical and fraternal twins, suggest that heredity plays a strong role in structuring the perisylvian cortex. Gray matter volumes in perisylvian areas are under tight genetic control and are highly heritable<sup>88, 89</sup>. Gyrus/sulcal patterns appear much less heritable<sup>90, 91</sup> (Thompson et al., 2002). Studies of monozygotic twins (who are genetically identical) reveal low intraclass correlations for the planum asymmetry index<sup>41</sup> ( $r = 0.2$ ). Nonetheless, low statistical power may preclude detection of these genetic effects<sup>88, 92</sup>.

Laterality cannot be influenced exclusively by an individual's genotype, as many identical twins are discordant for handedness and differ considerably in planum asymmetry<sup>93</sup>. A recent study of twins discordant for handedness found that genetic factors influenced the left and right hemisphere volumes twice as strongly in right-handed twin pairs, relative to discordant pairs. The decrement in genetic control of cerebral volumes in the non-right-handed pairs supports the notion of a “right-shift” genotype<sup>11</sup> that is lost in non-right-handers, resulting in decreased cerebral asymmetry<sup>94</sup>. Whatever the genetic determinants of laterality, many pre- and postnatal (but non-genetic) factors modulate anatomical and functional asymmetry. These include asymmetrical brain damage<sup>95</sup>, embryonic position in utero<sup>84</sup>, chemical and genetic gradients<sup>96</sup>, and fetal testosterone effects<sup>97</sup>. Laland et al.<sup>98</sup> proposed a population genetics model of handedness incorporating both genetic and environmental factors. They suggested that cultural factors brought to bear by parents on their children can strongly influence a child's handedness, perhaps to an even greater degree than genetic influences. This environmental factor complicates the arguments for strictly Mendelian inheritance of handedness, or for a genetic “right-shift” factor as the overriding determinant of handedness.

**Laterality and Gender.** Several studies have pointed to differences in brain asymmetry between men and women, some suggesting that the male brain may be, on average, more lateralized or asymmetrical than the female brain<sup>99</sup>. In tests designed to assess perceptual asymmetries (see ‘Dichotic Listening’, below), some studies report a greater lateralization of auditory or visual processing skills in men than women<sup>100, 101</sup>. Kimura<sup>102</sup> suggests that this may mean either (1) that the functions of the hemispheres may not be as sharply differentiated in women as in men, or alternatively (2) that larger commissural systems in women may act to reduce the difference in response scores between hemispheres. Whichever of these possibilities is true, sex differences in brain organization, both within and between hemispheres, are thought to underlie sex differences in motor and visuospatial skills, linguistic performance, and vulnerability to deficits following stroke and other focal lesions<sup>102</sup>. Sex differences have also been reported in the structural asymmetry of the planum temporale, with greater asymmetries in males<sup>103</sup>, but these findings have been contested. A more robust sex difference appears in the anatomy of the planum parietale, another asymmetric structure in the parietal lobe, at the posterior end of the Sylvian fissure. This structure is typically larger on the right hemisphere, and in right handers this asymmetry is greater in men, but in left handers the asymmetry is greater in women<sup>103</sup>. How these asymmetries might relate to differences in visuospatial processing are not yet understood.

**Hormonal Effects on Asymmetry.** In animal studies, more pervasive sex differences have been found in the pattern of structural brain asymmetries, and their determinants are better understood. In male rats, the right neocortex is thicker than the left, and females display a non-significant trend towards the opposite pattern<sup>104</sup>. The male asymmetry is mediated in part by early androgen exposure, as castration at birth, which prevents the flow of androgens from the testis to the brain, blocks the formation of the normal rightward brain asymmetry. The female pattern can be reversed to the male pattern by neonatal ovariectomy. Maternal environmental or nutritional stress also reverses the male-typical asymmetry to the female pattern in fetal male rats; it

both shifts and depresses a testosterone surge that normally occurs on gestational day 18105. These findings suggest that levels of androgenic and ovarian sex steroids, before and after birth, play a role in modulating brain asymmetry, at least in rodents. Their modulatory effects on rates of cell death and axon elimination are also likely to be sex specific106. Finally, the masculinizing effect of androgens on male cortical asymmetry appears to be mediated by their conversion to estrogen, rather than testosterone acting directly, as the effect is blocked by aromatase blocker ATD (1,4,6-androstatriene-3,17-dione107).

It is less clear, however, whether these sex specific asymmetries are found in humans. In human male fetuses a larger right hemisphere volume has been identified, but so far no equivalent pattern has been reported in adults102. In their widely-cited theory of cerebral lateralization, Geschwind and Galaburda51 suggested that elevated testosterone effects may be responsible for deviations from the normal dominance pattern (i.e. right-handed and leftward language dominance, as well as rightward visuospatial dominance). According to the theory, if testosterone levels are higher than normal in utero, consequences include masculinization, a smaller left hemisphere, and even anomalous dominance, due to a delay of left hemispheric growth. This model was posited to explain the different maturational rates of the sexes (with females generally maturing faster34), and the relative male superiority in right-hemisphere visuospatial tasks and female superiority in left-hemisphere linguistic tasks108. It may also explain the greater incidence of left-handedness in males109. The role of androgens in modulating brain asymmetry is attractive, given their key role in inducing other neuroanatomical sex differences in humans and other species110, 111.

**Functional Adaptation.** Experience-dependent plasticity and asymmetric behaviors may also induce different neuronal changes in the two hemispheres. In rats, the asymmetric use of only one forelimb in the post-weaning period induces an asymmetrically larger neuropil volume and lower cell packing density in the motor cortex112. In mice with a hereditary asymmetry in their whisker pads, a dominant right whisker pad has been associated with left paw preference113. Limb preference may therefore be associated with asymmetries in sensory input, although it is not known whether this relationship is causal. These findings suggest that some brain asymmetries are not necessarily genetically determined, and may result from lateralized sensory stimulation in pre-and post-natal development.

#### **Aberrant Asymmetries and Disease.**

Reduced planum volume asymmetries have been reported in some subjects with reading disorders or developmental dyslexia114-116Galaburda, 1995) and in some people with an unusual right-hemisphere dominance for speech. Hynd et al.114 reported a reversed planar asymmetry (i.e. right larger) in 9 of 10 right-handed dyslexic children studied with MRI. Dyslexics with phonological processing deficits also show reduced planum asymmetry115. Analogously, functional MRI studies reveal a pattern of brain activation in stutterers that is shifted towards the right in both motor and auditory language areas. This may suggest an inherent difference in the way in which normal subjects and stutterers process language117. Controversy surrounds reports of reduced or altered planar asymmetry in schizophrenia118, 119, 43. At the same time, there is great interest in the perisylvian region in schizophrenia, as it houses the primary auditory cortex, which may be implicated in auditory hallucinations120.

**Disease processes may also interact** with existing brain asymmetries or exacerbate them. An increased asymmetry of cerebral function in males is thought to underlie the greater male incidence of language impairment following stroke, and possibly also the increased incidence of learning disorders in males. The right hemisphere has a larger blood supply overall than the left121, and there is a higher mortality in cases of similar but right sided hemispheric lesions122.

**Some diseases also progress asymmetrically.** Patients with semantic dementia generally show asymmetric anterolateral temporal atrophy (typically worse on the left side) with relative sparing of the hippocampal formation. In Alzheimer's disease, a spreading wave of gray matter loss emerges initially in entorhinal and temporal-parietal cortices, sweeping into frontal and ultimately sensorimotor territory as the disease progresses123, 124. This sequence occurs in both hemispheres, but left-hemisphere regions are affected earlier and more severely. The right hemisphere following a similar pattern roughly two years later. Sylvian fissure CSF volumes also rise more sharply on the left than the right in dementia (left 32% higher, but on the right only 20% higher than controls125). PET studies also show left-greater-than-right metabolic dysfunction in early dementia126, 127 Corder et al., 1997). These disease process asymmetries suggest either (1) that the left hemisphere is more susceptible than the right to neurodegeneration in AD, or (2) that left hemisphere pathology results in greater structural change and lobar metabolic deficits126.